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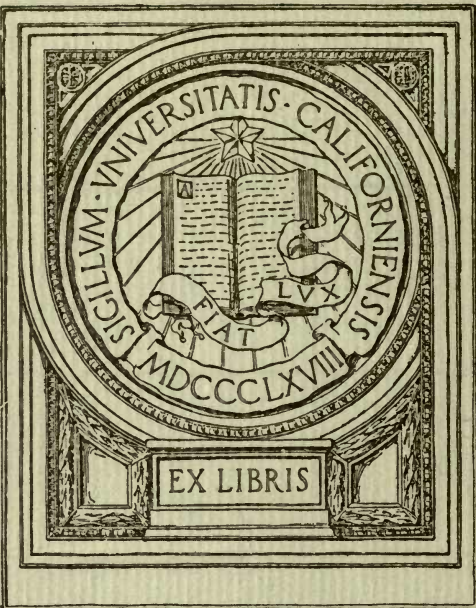


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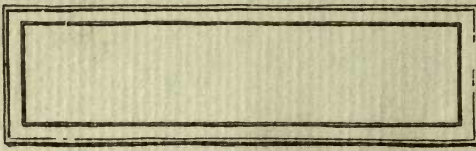
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7-Chloro-7,12-Dihydro- γ -Benzo-Phenarsazin
and Some of Its Derivatives

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

C. S. HAMILTON

EASTON, PA.:
PRESS OF THE ESCHENBACH PRINTING CO.
1922

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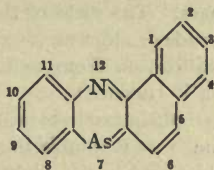
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7-CHLORO-7,12-DIHYDRO- γ -BENZO-PHENARSAZIN AND SOME OF ITS DERIVATIVES.¹

Of the nuclear heterocyclic arsenic compounds, that is, containing arsenic in the ring, those resulting from the condensation of arsenic chloride with diphenyl ether,² and with diphenylamine³ together with their respective derivatives have been described. The German patent mentions the similar compounds formed with β,β -dinaphthylamine, *p*-ditolylamine, α,α -dinaphthylamine and *p*-oxy-diphenylamine, but the products or their derivatives are not described. Grüttner and Wiernik⁴ prepared phenyl-arsino-pentamethylene and Grüttner and Krause⁵ phenyl-arsino-tetramethylene. Of the heterocyclic arsenical compounds containing two nuclear arsenic atoms, arsanthren or diphenylene-diarsin and its derivatives have been prepared by Kalb.⁶

This investigation had for its purpose the preparation of additional compounds of this type, particularly those resulting from the condensation of arsenic trichloride with diphenyl methane, benzophenone, its oxime, diphenyl sulfide, diphenylhydrazine and phenyl- α -naphthylamine. Results were negative except with diphenyl-hydrazine which yielded 6-chloro-phenarsazin, and phenyl- α -naphthylamine which yields 7-chloro-7,12-dihydro- γ -benzo-phenarsazin.

The hypothetical parent compound for the following derivatives would be γ -benzo-phenarsazin.



It is interesting to note that the 7-chloro derivative is much less irritating physiologically than the corresponding diphenyl-chloro-arsine,

¹ This work was done under a grant from the Interdepartmental Social Hygiene Board, Washington, D. C., Dr. T. A. Storey, Secretary. Some of the water-soluble products are being tested by Dr. A. S. Loevenhart of the University of Wisconsin, for their pharmaceutical value.

² Lewis, Lowry and Bergeim, *J. Am. Chem. Soc.*, **43**, 891 (1921).

³ A. Contardi, *Giorn. chim. applicata*, **2**, 100 (1920); *C. A.* **14**, 2628 (1920); Ger. pat. 281,049, Friedländer, **12**, 843; Wieland, *Ann.*, **423**, 1 (1921).

⁴ Grüttner and Wiernik, *Ber.*, **48**, 1479 (1915).

⁵ Grüttner and Krause, *ibid.*, **49**, 440 (1916).

⁶ Kalb, *Ann.*, **423**, 39 (1921).

6-chloro-phenarsazin or 6-chloro-phenoxarzin. Moreover, it possesses to a marked degree the property, not shown by the others, of forming stable alkoxy derivatives of the type $>As-OR$.⁷ The series of derivatives from methoxy to *n*-butoxy, not including the *iso*-propoxy which apparently forms with great difficulty, also the phenoxy and benzyloxy, are here described. These compounds are formed by adding in excess the respective alcohols treated with metallic sodium to a hot xylene solution of 7-chloro-7,12-dihydro- γ -benzo-phenarsazin. The excess of sodium alcoholate and the resulting sodium chloride are removed by filtration and the filtrate concentrated to crystallization. The products are all recrystallizable from hot xylene, and have sharp melting points ranging from 209° to 152° (uncorr.). They are attacked by 10% sodium hydroxide solution setting free the alcohol. They are all soluble in carbon tetrachloride, glacial acetic acid and acetone which are good recrystallizing agents. An alcohol other than that corresponding to the alkoxy group present cannot be used for purification as replacement of the alkyl results. Similarly, attempted recrystallization of an alkoxy derivative with aqueous phenol gives the phenoxy compound.

Experimental.

7-Chloro-7,12-dihydro- γ -benzophenarsazin, $HN \begin{array}{c} \diagup C_{10}H_8 \\ \diagdown C_6H_4 \end{array} AsCl$.—Eighty-eight g.

of phenyl- α -naphthylamine and 80 g. (10% excess) of redistilled arsenic trichloride were heated under a reflux condenser. The mixture commenced to boil at $165-170^{\circ}$ with evolution of hydrogen chloride. The boiling temperature gradually rose to 200° when the evolution of hydrogen chloride had practically ceased. The time required to reach this temperature was about 2 hours. Upon cooling the reaction mixture solidified to a greenish-yellow mass. The yield of the crude product was 115 g., 87% of the calculated amount. The crude product was recrystallized from xylene and washed with alcohol. A second recrystallization from xylene yielded fine needles, canary-yellow in color and melting at 219° (uncorr.).

7-Chloro-7,12-dihydro- γ -benzophenarsazin is insoluble in water and is not attacked by 6 *N* sodium hydroxide solution. It is soluble in xylene, glacial acetic acid, alcohol, benzene, and carbon tetrachloride, and has a slightly irritating effect on the mucous membranes of the nose and throat. The best solvent for recrystallization is xylene in which it is 5% soluble.

Analyses. Subs., 0.1995, 0.2018: 15.88, 16.20 cc. of 0.0765 *N* iodine sol. Calc. for $C_{16}H_{11}NClAs$: As, 22.90. Found: 22.83, 23.07.

Subs., 0.1544, 0.1756: AgCl, 0.0655, 0.0786. Calc. for $C_{16}H_{11}NClAs$: Cl, 10.82. Found: 10.48, 11.05.

7-Methoxy-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \diagup C_{10}H_8 \\ \diagdown C_6H_4 \end{array} As-OCH_3$.—Sodium

methylate, prepared by dissolving 1.4 g. of clean metallic sodium in 50 cc. of absolute methyl alcohol, was added to 9 g. of 7-chloro-7,12-dihydro- γ -benzophenarsazin

⁷ Cf. Michaelis, *Ann.*, 321, 143 (1902); Wieland and Rheinheimer, *Ann.*, 423, 1 (1921).

dissolved in 200 cc. of hot xylene. The mixture was heated under a reflux condenser for 10 minutes. The excess of sodium methylate and the sodium chloride produced in the reaction were filtered hot. Upon cooling, the filtrate remained clear. Approximately 100 cc. of xylene was removed by distillation under reduced pressure. On cooling, almost colorless crystals of the methoxy compound were deposited. This was recrystallized from xylene. The yield was 8 g. or 89%. The product melts at 209° (uncorr.) and is soluble in benzene, carbon tetrachloride, and acetone, but insoluble in water. It is decomposed by 10% sodium hydroxide.

Analyses. Subs., 0.2092, 0.2102: 24.54, 24.99 cc. of 0.0521 *N* iodine sol. Calc. for $C_{17}H_{14}ONAs$: As, 23.22. Found: 22.92, 23.23.

7-Ethoxy-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \text{C}_{10}\text{H}_6 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array} \text{As} - \text{OC}_2\text{H}_5$.—This

compound was prepared in a similar manner, using sodium ethylate. The yield was 76%. The compound melts at 165° (uncorr.) and when recrystallized from absolute ethyl alcohol gives colorless crystals which turn slightly yellow on standing. It is soluble in the common organic solvents and is decomposed by a 10% sodium hydroxide solution.

Analyses. Subs., 0.2005, 0.1998: 22.60, 22.49 cc. of 0.0521 *N* iodine sol. Calc. for $C_{18}H_{16}ONAs$: As, 22.25. Found: 22.02, 21.99.

7-*n*-Propoxy-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \text{C}_{10}\text{H}_6 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array} \text{As} - \text{OC}_3\text{H}_7$.—This

compound was obtained by treating 9 g. of 7-chloro-7,12-dihydro- γ -benzophenarsazin with an excess of sodium *n*-propylate. A yield of 7.3 g. (74%) of pale yellow crystals resulted. The compound melts at 152° (uncorr.), is soluble in benzene, acetone and carbon tetrachloride, and is attacked by hot alkalis.

Analyses. Subs., 0.2023, 0.1970: 22.28, 21.52 cc. of 0.0521 *N* iodine sol. Calc. for $C_{19}H_{18}ONAs$: As, 21.36. Found: 21.52, 21.34.

7-*n*-Butoxy-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \text{C}_{10}\text{H}_6 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array} \text{As} - \text{OC}_4\text{H}_9$.—This

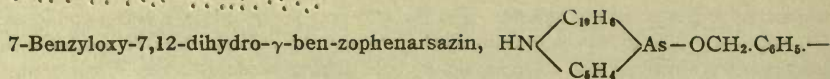
compound was obtained by the action of an excess of sodium *n*-butylate on 9 g. of 7-chloro-7,12-dihydro- γ -benzophenarsazin dissolved in 200 cc. of xylene. The yield was 6.7 g., or 67%. The almost colorless product is soluble in benzene, acetone and glacial acetic acid. It is decomposed by 10% sodium hydroxide solution. The compound softens slightly at 120° but does not melt completely even at 260°. The same results were obtained with samples prepared from crude *n*-butyl alcohol and the c. p. alcohol.

Analyses. Subs., 0.1997, 0.2002: 20.95, 20.93 cc. of 0.0521 *N* iodine sol. Calc. for $C_{20}H_{20}ONAs$: As, 20.54. Found: 20.49, 20.42.

7-Phenoxy-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \text{C}_{10}\text{H}_6 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array} \text{As} - \text{OC}_6\text{H}_5$.—So-

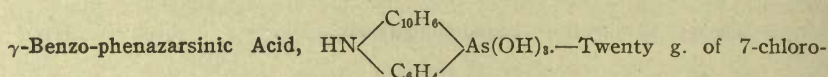
dium phenolate was prepared by dissolving 1.4 g. of metallic sodium in a solution of 8 g. of phenol in 30 cc. of absolute ethyl ether. This was added to 9 g. of 7-chloro-7,12-dihydro- γ -benzo-phenarsazin in 200 cc. of xylene, and the usual procedure followed. The compound was deposited in fine yellow needles. The yield was 6.5 g. or 61%. The product melts at 179° (uncorr.), is soluble in the common organic solvents, and readily attacked by a 10% solution of sodium hydroxide.

Analyses. Subs., 0.1973, 0.2021: 19.50, 20.03 cc. of 0.0521 *N* iodine sol. Calc. for $C_{22}H_{16}ONAs$: As, 19.48. Found: 19.31, 19.36.



By following the above procedure the compound was prepared by adding an excess of sodium benzyolate to 9 g. of 7-chloro-7,12-dihydro- γ -benzophenarsazin in xylene solution. A yield of 7.3 g., or 67% was obtained. The almost colorless compound melts at 154° (uncorr.). It is soluble in benzene, glacial acetic acid and carbon tetrachloride.

Analyses. Subs., 0.2042, 0.2119: 19.55, 20.32 cc. of 0.0521 *N* iodine sol. Calc. for $\text{C}_{23}\text{H}_{18}\text{ONaAs}$: As, 18.72. Found: 18.70, 18.74.



7,12-dihydro- γ -benzo-phenarsazin was dissolved in 800 cc. of glacial acetic acid. To this solution 100 g. of a 3% solution of hydrogen peroxide was added and the whole heated under a reflux condenser for 15 minutes. When the solution had cooled, the acid crystallized in almost colorless needles. The crude product was recrystallized from glacial acetic acid. The yield was 17 g., or 81% of the calculated amount.

The acid does not melt below 260°. It is insoluble in all the common organic solvents, with the exception of glacial acetic acid, and soluble in alkalis in the cold.

Analyses. Subs. (dried at 120° for 10 hrs.), 0.2117, 0.1986: 23.40, 22.11 cc. of 0.0521 *N* iodine sol. Calc. for $\text{C}_{16}\text{H}_{14}\text{O}_3\text{NAs}$: As, 21.86. Found: 21.59, 21.79.

When the acid is heated to constant weight at 150° it loses one molecule of water giving a form of the arsinic acid containing the more usual grouping $>\text{As}(\text{O})\text{OH}$.

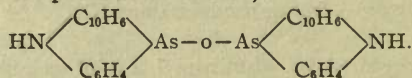
Analyses. Subs. (heated to const. wt. at 150°), 0.2312, 0.2146: 31.72, 29.35 cc. of 0.0445 *N* iodine sol. Calc. for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{NAs}$: As, 23.07. Found: 22.90, 22.83. Loss on heating at 150°. Subs., 0.4218, 0.4059: wt. lost, 0.0215, 0.0209. Calc. for 1 H_2O : 5.24. Found: 5.09, 5.13.

The sodium salt of γ -benzo-phenazarsinic acid was prepared in the following manner. Five g. of γ -benzo-phenazarsinic acid was dissolved in a solution of 0.1 *N* sodium hydroxide. The solution was filtered and concentrated to a small volume on the steam-bath. Upon cooling, the sodium salt was deposited in needle-like crystals, pink in color. After several recrystallizations from 95% alcohol an almost colorless product was obtained. The yield was 5.2 g., or 85%. The sodium salt does not melt below 260°. It is soluble in water (5%), in alcohol and acetone and is quite hygroscopic. It is insoluble in benzene and xylene.

Analyses. Subs., 0.2013, 0.2209: 18.40, 19.95 cc. of 0.0521 *N* iodine sol. Calc. for $\text{C}_{16}\text{H}_{11}\text{O}_2\text{NAsNa} \cdot 4\text{H}_2\text{O}$: As, 17.89. Found: 17.86, 17.65.

Subs., 0.4527, 0.4853: wt. lost at 150°, 0.0769, 0.0818. Calc. for 4 H_2O : 17.18. Found: 16.99, 16.86.

7,12-Dihydro- γ -benzo-phenarsazin-7-oxide,



—Five g. of 7-chloro-7,12-dihydro- γ -benzo-phenarsazin was dissolved in 100 cc. of xylene, and to this was added a solution of 2 g. of freshly prepared silver oxide in 50 cc. of ammonium hydroxide. The slightly yellow oxide precipitated immediately. After heating under a reflux condenser for a few minutes the oxide was filtered hot and washed free from silver with ammonium hydroxide. The yield was 4 g., or 90%. The oxide does not darken or melt below 250°, is soluble in glacial acetic acid and insoluble in benzene, xylene, and carbon tetrachloride.

Analyses. Subs., 0.2011, 0.2005: 25.61, 25.49 cc. of 0.0521 *N* iodine sol. Calc. for $C_{32}H_{22}ON_2As_2$: As, 25.00. Found: 24.88, 24.84.

7-Bromo-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \diagup C_{10}H_6 \\ \diagdown C_6H_4 \end{array} As-Br$.—Five g. of

7-phenoxy-7,12-dihydro- γ -benzo-phenarsazin was heated under a reflux condenser for 4 hours with an excess of conc. hydrobromic acid. The green, crude product was recrystallized several times from xylene, yielding dark yellow needles. The yield was 3.6 g. or 75%. The crystals melt at 227° (uncorr.). The compound is soluble in benzene, toluene, xylene and glacial acetic acid. It is insoluble in water and is not acted upon by dilute alkalis.

Analyses. Subs., 0.1999, 0.1991: 20.41, 20.46 cc. of 0.0521 *N* iodine sol. Calc. for $C_{18}H_{11}NBrAs$: As, 20.16. Found: 19.95, 20.08.

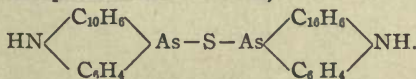
7-Iodo-7,12-dihydro- γ -benzo-phenarsazin, $HN \begin{array}{c} \diagup C_{10}H_6 \\ \diagdown C_6H_4 \end{array} As-I$.—Three g. of

7,12-dihydro-7-phenoxy- γ -benzo-phenarsazin was refluxed for 4 hours with a solution of hydriodic acid made by adding 10 g. of conc. hydriodic acid to 90 cc. of distilled water. The crude product was dark red in color. Upon recrystallization from xylene, beautiful red needles were obtained. The yield was 2.5 g. or 62%. This compound was also prepared in the above manner by heating 7,12-dihydro- γ -benzo-phenarsazin-7-oxide with hydriodic acid. The compound melts at 205° (uncorr.), is soluble in benzene, xylene, toluene and glacial acetic acid.

Analyses. Subs., 0.2043, 0.1953: 22.15, 21.35 cc. of 0.0445 *N* iodine sol. Calc. for $C_{18}H_{11}NIAs$: As, 17.90. Found: 18.10, 18.24.

Subs., 0.1954, 0.2123: AgI , 0.1082, 0.1183 g. Calc. for $C_{18}H_{11}NIAs$: *I*, 30.21. Found: 29.96, 30.14.

7,12-Dihydro- γ -benzo-phenarsazin-7-sulfide,



—Three g. of 7-chloro-7,12-dihydro- γ -benzo-phenarsazin was dissolved in 500 cc. of absolute ethyl alcohol and hydrogen sulfide bubbled through the solution. A yellow precipitate was formed immediately. As it was insoluble in all common organic solvents the impurities were removed by refluxing with xylene. The yield was 2 g., or 71%. The compound melts at 204–5° (uncorr.).

Analyses. Subs., 0.1980, 0.2001: 25.61, 26.03 cc. of 0.0497 *N* iodine sol. Calc. for $C_{32}H_{22}N_2As_2S$: As, 24.35. Found: 24.12, 24.26.

Condensation of Diphenylhydrazine and Arsenic Trichloride.

Ten g. of diphenylhydrazine was treated with 12 g. of arsenic trichloride which had been cooled to 5°, and the mixture gently warmed under a reflux condenser. At 34° the reaction became violent and the temperature rose at once to 105°. The mixture began to boil at 130–135° and in the course of 2 hours the boiling temperature rose to 210°, when yellowish vapors appeared in the flask. Upon cooling the reaction mixture solidified to a black granular mass. Recrystallization from xylene gave 8.5 g. of greenish-yellow crystals. Upon recrystallization from carbon tetrachloride fine yellow needles, melting at 192° (uncorr.), were obtained. The compound has the properties and composition of 6-chloro-phenarsazin.

The formation of this compound may be explained by the fact that diphenylhydrazine, at its boiling point, decomposes in part to form diphenylamine and other products.⁸ Part of the arsenic chloride, in all probability, acts as a reducing agent and hastens the reaction at a lower temperature. The diphenylamine thus formed then condenses with arsenic trichloride to form 6-chloro-phenarsazin.

Subs., 0.2030, 0.2200: 30.80, 33.30 cc. of 0.0479 *N* iodine sol. Calc. for $C_{12}H_9NAsCl$: As, 27.02. Found: 27.29, 27.23.

Subs., 0.4053, 0.4207: 13.98, 13.94 cc. of 0.1 *N* HCl. Calc. for $C_{12}H_9NAsCl$: *N*, 5.04. Found: 4.83, 4.85.

Summary.

1. A brief summary of the chemistry of the nuclear heterocyclic arsenic compounds is presented.

2. The condensation of phenyl- α -naphthylamine with arsenic chloride, and the properties of the resulting 7-chloro-7,12-dihydro- γ -benzo-phenarsazin are described.

3. The methods of preparation and the properties of the following derivatives of 7-chloro-7,12-dihydro- γ -benzo-phenarsazin are given: 7-methoxy-7,12-dihydro- γ -benzo-phenarsazin; 7-ethoxy-7,12-dihydro- γ -benzo-phenarsazin; 7-*n*-propoxy-7,12-dihydro- γ -benzo-phenarsazin; 7-*n*-butoxy-7,12-dihydro- γ -benzo-phenarsazin; 7-phenoxy-7,12-dihydro- γ -benzo-phenarsazin; 7-benzyloxy-7,12-dihydro- γ -benzo-phenarsazin; γ -benzo-phenaz-arsinic acid; 7,12-dihydro- γ -benzo-phenarsazin-7-oxide; 7-bromo-7,12-dihydro- γ -benzo-phenarsazin; and 7,12-dihydro- γ -benzo-phenarsazin-7-sulfide.

The author wishes to thank Dr. W. Lee Lewis for suggesting this investigation, and for criticism and advice given throughout the course of this work.

⁸ Stahel, *Ann.*, 258, 244(1890).

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